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EXAMINER	
SCHWADRON, R	
ART UNIT	PAPER NUMBER
1644	37

DATE MAILED: 06/24/98

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☒ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 5/14/98 and 5/4/98 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: none
   Claims objected to: N/A
   Claims rejected: 40-42, 45-47

   However;

   ☒ Applicant's response has overcome the following rejection(s): see enclosed Office note

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because the rejections as enunciated in the enclosed note remain for reasons of record.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other SEE ENCLOSED NOTE

6/22/98

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800 1644

PTOL-303 (REV. 5-89)

6. Claims 40-42,45-47 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in paragraph 18 of the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

There is no support in the specification as originally filed for the recitation of "essentially free from contaminating Fc" in claims 40 and 45. The specification and original claims 27 and 29 do not recite that the claimed F(ab) are essentially free from contaminating Fc. They recite that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

Regarding applicants comments, there is no disclosure in the specification as originally filed that the claimed F(ab) are essentially free from contaminating Fc. The specification discloses that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen. There is no disclosure in the specification as originally filed of the scope of the claimed invention wherein the claimed invention is essentially free from contaminating Fc. Regarding applicants comments about the four-hour digest in Figure 4 of the specification, said preparation is not essentially free from contaminating Fc because it contains detectable levels of Fc. Furthermore, the particular experiment which applicant refers to discloses a particular preparation generated under a particular set of conditions. There is no support in the specification as originally filed of the scope of the claimed invention. There is no written description of the scope of the claimed invention in the specification as originally filed.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 40-42,45-47 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical

Dictionary (1977) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Regarding the Russell declaration filed 5/4/98, the following comments are made. Coulter et al. teach that F(ab) which neutralizes a large molecular weight protein snake toxin can be made and that said antivenom can work in vivo to neutralize snake toxin (see page 202, third paragraph). Smith et al. teach that Fab fragments can be used to neutralize digoxin (low molecular weight potential toxin)(see *Summary*). Smith et al. also teaches that relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance (see page 393, *Discussion* section) indicating that Smith et al. believed that Fab could be used for the neutralization of toxic substances other than digoxin. Furthermore, Smith et al. indicated that Fab and the intact antibody from which the Fab were derived would be expected to have similar binding properties (see page 393, *Discussion* section). Thus, the art recognized that when an intact antibody has been shown to have the capability of neutralizing a toxin, that the Fab derived from said antibody will also be able to neutralize said toxin. Furthermore, based on the teachings of Coulter et al. and Smith et al. it appears that use of Fab to neutralize toxin (wherein the intact antibody had already been shown to be capable of neutralizing said toxin) would be equally applicable to large and small toxin molecules. Regarding the Faulstich et al. reference said reference teaches that monoclonal antibody against alpha amatoxin cannot be used to treat alpha amatoxin and that F(ab) obtained from said antibody also cannot be used to treat alpha amatoxin. Thus, the circumstances surrounding treatment of alpha amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Regarding comments about Balthasar et al., Balthasar et al. refer to alpha amatoxin, which is a toxin which cannot be treated with antibodies as shown by Faulstich et al. The circumstances surrounding treatment of alpha amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Furthermore, Balthasar et al. teach that the use of drug-binding antibodies and antibody fragments for the treatment of drug intoxication is well known. (see Abstract, last sentence). Thus, there are no negative teachings in Faulstich et al. or Balthasar et

al. that would suggest that F(ab) antivenin could not be used to treat snake venom poisoning. Regarding various comments in pages 8-12 of the Russell declaration as to why it would be unpredictable as to whether the Fab antivenom of the claimed invention would work in vivo, there is no disclosure in the Russell declaration of any reference which states that Fab fragments could not neutralize toxin wherein the fragments were derived from an antibody that had been previously shown to neutralize the toxin, and based on the teachings of Coulter et al. and Smith et al. it appears that use of Fab to neutralize toxin (wherein the intact antibody had already been shown to be capable of neutralizing said toxin) would be equally applicable to large and small toxin molecules. Regarding comments in the Russell declaration about Coulter et al., the art already recognized that intact antibody against Crotalus snake venom could be used to treat Crotalus snake venom in vivo. The Smith et al. reference indicates that Fab actually have a more favorable distribution in vivo than intact antibody in that Fab can be found in particular anatomical compartments such as the extravascular space wherein intact antibody occurs in smaller concentrations. Regarding comments about Sorkine et al., Sorkine et al. disclose that Fab was successfully used to neutralize toxin in vivo and that "One explanation is the different kinetics of these fragments. The smaller size of Fab results in faster diffusion and a greater volume of distribution". Thus, Sorkine et al. confirm the teachings of Smith et al. that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. Regarding applicants comments about Sorkine et al., Coulter et al. teach that Fab work in vivo to neutralize a snake toxin. Regarding the fact that the toxin and antibody were first mixed before in vivo injection, the art already recognized that the antivenom from which the Fab would have been derived could bind Crotalus venom, and Smith et al. reference indicates that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. Furthermore, Sorkine et al. actually confirm that with regards to Fab that the in vitro mixture of the antibody and toxin prior to administration mirrors the effect seen when Fab and toxin are administered separately in vivo. Regarding applicants comments, antisera against Crotalus toxin which contained antibodies to neutralize said toxin/toxins was already known in the art. Smith et al. teach that F(ab) are less immunogenic than the antibody from which they are derived (see page 395). Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab

fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG." (page 393).

9. Claims 45-47 remain rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants arguments as they apply to the instant rejection, the claimed invention under consideration is not drawn to an antivenom. It is drawn to a Fab antibody. Whether or not an antivenom based on the Fab recited in the claims could be used to treat snake bites in vivo is not germane to the claimed invention because the claimed Fab can be used in vitro assays. Coulter et al. teach that: "Fab fragments of IgG have been used in enzyme immunoassay instead of IgG (Kato et al. 1976). EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme." (page 199, first paragraph).

10. The rejection of claims 40-42,45-47 under 35 U.S.C. 102(a) as being anticipated by Sullivan et al. (Veterinary and Human Toxicology) for the reasons elaborated in the previous Office Action is withdrawn in view of the second Russell declaration filed 5/4/98.

11. Regarding applicants request for an interview, applicant is invited to call the Examiner and schedule an interview.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 305-3014.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail

service. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ms Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644
June 23, 1998